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NANO-POWERED NANOROBOTS OFFER PROMISES IN GENE THERAPY AND NANOMEDICINE

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Abstract

Cancer-fighting, blood-roaming Nanorobots have the potential to transform our lives, but they have yet to demonstrate their use in real-world settings. This review describes the requirements for a nanomotor to survive the in vivo environment, locate its targets, operate as needed, and terminate when the mission is complete. A nanorobot should be the proper size, constructed of biocompatible or biodegradable materials, and capable of rapid, autonomous propulsion through a network of blood arteries with a flow rate of about cm s1. A major transformation of the existing system is now required, since progress is reported across multiple laboratories and in different areas. Other options exist, such as hybrid nanomotors that combine chemotaxis with biological propulsion.

1 Introduction

The concept of functional nanorobots has been used by generations of scientists and engineers who have pushed the boundaries of technology. Fast forward 60 years, and advances in nanoscopic precision manufacturing, as well as our knowledge of chemistry and physics at nanoscales, have resulted in prototype nanorobots that can move, rotate, pick, release, lead, follow, cut, and disintegrate at a size smaller than cells. [1-12] The nanorobot revolution is already being heralded by optimistic scholars and the general public. [13]

Despite an increase in the number of publications in the previous decade, the majority of reported nanorobot applications are still "proof-of-concepts" or "preliminary demonstrations" that are frequently too crude and restricted for practical implementations. Although the situation is progressively improving, with a growing amount of in vivo research aimed at real-life settings (see our discussion below), clinical translation of nanorobots remains a challenge. Furthermore, as we will see later, the majority of nanorobot advances in vivo [15] [24-27] (or ex vivo [28, 29]) are linked to operations in easily accessible regions of human bodies, such as the digestive tract, [25] bladder, skin, or the eyes (ex vivo).28, 29 Nanorobots that go into the bloodstream are uncommon, and they're usually propelled by magnetic fields. [30] As expectations rise and final products remain unreleased, a sense of urgency and anxiety develops among nanorobot researchers (including ourselves), and rightly so.

This significant gap between our current capabilities and the optimal concept forces us to take a hard look at where we are now and where medical nanorobot research is headed. In light of this requirement, this paper focuses on a variety of basic and practical difficulties that stymie the translation of nanorobots from benchtop research to clinical use. We describe the various challenges that a nanomotor faces while attempting to Survive, Locate, Operate, and Terminate (abbreviated as "SLOT") inside the human body, focusing on a popular type of nanorobot (synthetic colloidal swimmers, or "nanomotors," see below for a detailed description), and using targeted cancer therapy as an example.We compare how the state-of-the-art in nanomotor research measures up to (or falls short of) what is necessary for a successful mission along the route of a SLOT mission. This explanation of SLOT is preceded by a brief introduction of nanomotors and targeted cancer therapy for those unfamiliar with these ideas, which was inspired by an outstanding review article on the voyage of cancer-targeting nanoparticles [31]. To wrap up our adventure, we'll go through one of the most important elements of making a medical nanorobot a reality: deciding on the best power source.

The objective of this essay, as well as other outstanding review papers on the subject [8], 32-40, is not to minimize the value of nanorobot (or nanomotor) research, or to dissuade students, faculty, funding agencies, or the general public from joining forces on a wonderful adventure. Rather, we argue that we are at a critical juncture in the creation of functioning nanorobots, with 20 years of progress behind us and a long road ahead. To win this struggle and keep this field of study from becoming mediocre, researchers working to make "Fantastic Voyage" a reality must establish a shared objective (for example, a really feasible nanomotor design for the whole SLOT trip) and devote our efforts to it. We specifically suggest that any "progress" reported in nanomotors for targeted cancer therapy be compared to our planned SLOT mission in order to assess its therapeutic utility.

Finally, we give a few observations on the article's impartiality and comprehensiveness. First, despite our best efforts to be objective, this Progress Report contains numerous comments and opinions that are by definition subjective. Readers of this review article should maintain a reasonable amount of skepticism, as with any other review article. Furthermore, unlike many review articles on this issue (see Section 2 for a list), this page focuses on the limitations, drawbacks, or flaws of current nanomotor research in the hopes that constructive criticism will provoke thinking and, eventually, benefit the community's healthy growth. Finally, this article is not intended to be exhaustive, and it does not purport to contain everything there is to know about medical nanorobots. This aim is beyond our capabilities, and it is also not reader-friendly. Rather, we've concentrated on a specific sort of nanorobot (i.e., "nanomotors") and a specific application (targeted cancer therapy). We have had to overlook a significant quantity of literature on other issues, as well as their exciting growth, as a result of this.

2 Nanomotors: What Are They and How Do They Work?

Medical nano/microrobots, in general, are tiny synthetic molecular machines that change configuration in response to environmental stimuli, [9, 11, 41]. as well as much bigger machines (dubbed "small-scale robots") that grasp, cut, detect, and maneuver like macroscopic robots. [42-45] This article, on the other hand, is about "nanomotors," which are small devices with sizes ranging from 100 nm to 10 m that are activated by chemical processes, electromagnetic waves, light, or ultrasound and float freely in fluids like bacteria or cells.[7, 46, 47] We chose nanomotors as our target because they are the closest thing to a optimal nanorobot in terms of size and functionality. This isn't to suggest that nanomotors are without flaws. In comparison to small-scale robots, they lack the intricacy of molecular machines and are frequently outfitted with limited mobility, controllability, and degree of freedom. These functions, on the other hand, may be built into a nanomotor by careful and creative material design. More significantly, as shown below, nanomotors are more likely than smaller or bigger counterparts to accomplish the SLOT mission of targeted cancer treatment. Therefore, we feel this article is worth reading even if you work with other forms of nano/microrobots.

Nanomotors have been around since the early twenty-first century, [48, 49], and have gone through several revisions that have progressively increased their diversity, performance, and functions. Research-level nano- and micromotors, unlike sci-fi versions of nanorobots, lack extended limbs, sharp claws, and gleaming eyes. Rather, they are typically shaped like a rod, sphere, tube, or helix, and are constructed of common materials, including metals, metal oxide, and polymers. [50] These ordinary-looking colloids burst into action at speeds of hundreds of body lengths per second or more when activated (see below). The dynamics of an autonomously swimming nanomotor are typically comparable to those of bacteria under an optical microscope, with ballistic runs broken by random twists. Nanomotors are considered biomimetic materials and are often utilized as model systems for the study of active matter because of this resemblance. [51] The strength of such lifelike action, which is important for its use in the task detailed below, derives from two sources (see our recent review articles [46, 47] on the details of each propulsion mechanism). Chemical reactions on the colloidal particle itself provide the first source of energy, [52-54], which either produces a concentration gradient of certain chemicals and thus induces slip flows on the surface of a nanomotor (a mechanism known as self-phoresis or auto-phoresis), or releases gas bubbles that propel a nanomotor like a jet plane. An external source of power for a nanomotor can be electric fields, magnetic fields, light, heat, or ultrasound. [55] In this article and in Section 4, the advantages and drawbacks of these two types of propulsion systems in vivo will be examined in greater depth.

A nanomotor can be directed, load and unload cargo, detect the surroundings, and apply mechanical forces after further functionalization, all of which are useful qualities for practical applications. [46] In this sense, a nanomotor satisfies the definition of a "robot," and is thus just as useful as its larger counterpart. A swarm of nanomotors can communicate and show biomimetic, collective behaviors such as schooling, predator-prey interactions, and chemical waves, in addition to being competent as individuals, through a number of ways, greatly increasing their use. It's no wonder, therefore, that nanomotors with these characteristics and benefits are a strong contender for medical nanorobots.

There are, however, certain limitations. For example, producing nanomotors in large quantities with desired properties is often difficult or expensive; [65] Many existing propulsion mechanisms are poorly biocompatible, not to mention inefficient; Brownian motion dominates at the nanoscales, but precise steering of a nanorobot is critical; [71] These and other issues are well-known, but they are far from being resolved. The remainder of this essay will focus on how these issues relate to the operation of a nanomotor in a "Fantastic Voyage," as well as what is required to make it a successful mission.

To wrap up this section and point readers to additional resources beyond this review, we've compiled a list of excellent review articles on nanomotors for biomedical applications on the following topics: 1) overall overviews, 2) nanomotors for biomedical applications, and 3) nanomotors for biomedical applications.

Drug distribution/cargo transportation, [32, 34, 38, 40, 76-81] 3) recognition, [82, 83, 77-79] 4) sensing 5) In vivo studies, [34, 84-86] 6) the use of a surface coating, [87] 7) cancer treatment [33, 37, 88, 89]. 8) biocompatibility, [66], which is a term that refers to the ability of a substance to 9) biological barriers/complex environment/entry into a cell 90-92 and 10) imaging, as well as specific types of biomedical nanomotors, such as those composed of hydrogel or those driven by magnetic fields. [96] This collection of 35 review papers (and counting) is by no means exhaustive, and it only covers the years 2013–2020. However, it should be apparent that medical nanomotors are a hot issue that is gaining traction, particularly in the areas of medication administration and/or cancer therapy.

3 Nanomotors and Targeted Cancer Therapy: A Case Study

A nanorobot, no matter how versatile it appears, is seldom a Swiss knife that can do everything well. Rather, a nanorobot should be designed with a specific set of capabilities that are suited to a particular application. [4] Targeted cancer treatment, particularly for solid tumors, has attracted the most interest from both academia and the general public, and is perhaps the holy grail for medical nanorobot development. As a result, we use it as an example to demonstrate the slew of scientific and engineering problems that come with using a nanomotor in medicine. Note that comparable problems exist in applications such as environmental sensing and cleanup, microfabrication, and nanomachines of various types, such as molecular machines and protein machines, albeit in different forms.

The idea behind targeted cancer chemotherapy in a solid tumor is that by delivering therapeutic chemicals selectively to cancer cells while avoiding healthy cells and tissues, cancer treatment efficacy may be considerably enhanced while adverse effects are greatly reduced. [97] This idea is linked to the advancement of nanomedicine, such as customized nanoparticles having medicinal and/or diagnostic capabilities. The absence of a clear passage from the blood stream to the center of a tumor, the dense collagen network (i.e., extracellular matrix [102]) within the tumor, and a hydraulic pressure higher within the tumor than outside, among other factors, place many practical constraints on the efficacy of nanomedicines. [31, 98, 103-105]; Despite decades of intensive study and laboratory achievement, only a tiny number of nanoparticle-based cancer-targeting medicines have been clinically successful due to these difficulties. One well-known limitation of nanoparticles for targeted cancer therapy is that they can only reach their target by convection and passive diffusion, which is inefficient in the dense tumor microenvironment with interstitial flow. [105]

Actively propelled nanomotors, loaded with chemotherapeutic medicines and externally directed, are envisioned as a good answer to the challenge of passive targeting, since they actively plough through the hostile tumor microenvironment while communicating with human operators. [32].

As a result, a slew of difficulties await, some of which are common to nanoparticles and others which are unique to nanomotors. To better understand these difficulties, we encourage readers to embark on a mental journey with a blood-roaming, cancer-fighting nanomotor, from its introduction into the human body to the conclusion of its mission, where challenges arise at every turn.

Before we get started, it's crucial to remember that cancer is only one of the medical diseases that a nanorobot (or a nanomotor) may help with. As a result, while the problems we address here are critical for cancer treatment, they may be entirely irrelevant to other medical diseases. Microsurgery in the digestive tract, such as microbiopsy on the inner surface of the stomach or intestine, is an excellent example. [16, 18, 85] A microrobot encounters chemicals and an overall environment that differ significantly from those encountered in cancer therapy, necessitating very different and distinct functions.This field of study merits its own examination [86], and it will not be covered in this article. On the other hand, substantial or intriguing advances achieved with microbots in applications beyond targeted cancer therapy are not always appropriate or inherently relevant to the SLOT mission below. In reality, despite the growing amount of research claiming the efficacy of nanomotors for biomedical applications, the majority of them are in vitro studies, with little progress being made with nanomotors for in vivo targeted cancer therapy.

3.1 Resilience

The most difficult element of developing an effective targeted cancer therapy is getting nanoparticles into people's bodies and keeping them there for as long as they're needed while still being helpful. For the same reason, a nanomotor's "survival" is critical, and it begins with its introduction into the patient's body.

First, it must be determined whether the nanomotor is swallowed [19, 20], or injected, i.e. whether the nanomotor enters the digestive tract [106] or the bloodstream.This option is very dependent on the nanomotor's goal, and it will have a significant impact on the problems that follow. Nanomotors will most likely be introduced into the bloodstream for our hypothetical goal of targeted cancer therapy.

A vast range of proteins in the blood plasma quickly coat the surface of a nanomotor once it enters the blood artery. [106-108] Most, if not all, nanomotors driven by chemical processes on the surface are essentially disabled by this "protein corona." Despite this, this disastrous outcome is rarely mentioned in the nanomotor literature.

The high ionic strength (salt concentration) of bodily fluids such as blood and interstitial fluids, which slow down significantly in solutions of millimolar salt or more, poses yet another critical challenge to nanomotors powered by chemical gradients (i.e., self-electrophoresis or diffusiophoresis) [109]. The nanomotor community has long been aware of this issue, [46, 109], but despite recent efforts to address it, [110], we are unaware of any sort of chemical gradient-powered nanomotor that advances beyond Brownian motion in actual biological fluids. Tubular nanomotors that move by ejecting gas bubbles appear to perform significantly better in this situation, though they are still plagued by the protein corona issue, and producing bubbles in the bloodstream isn't ideal (worse if a large group of gas-producing nanomotors is involved).There are, however, certain limitations. For example, producing nanomotors in large quantities with desired properties is often difficult or expensive; [65] Many existing propulsion mechanisms are poorly biocompatible, not to mention inefficient; Brownian motion dominates at the nanoscales, but precise steering of a nanorobot is critical; [71] These and other issues are well-known, but they are far from being resolved. The remainder of this essay will focus on how these issues relate to the operation of a nanomotor as well as what is required to make it a successful mission.

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Actively propelled nanomotors, loaded with chemotherapeutic medicines and externally directed, are envisioned as a good answer to the challenge of passive targeting, since they actively plough through the hostile tumor microenvironment while communicating with human operators. [32] But it's not as easy as that. As a result, a slew of difficulties await, some of which are common to nanoparticles and others which are unique to nanomotors. To better understand these difficulties, we encourage readers to embark on a mental journey with a blood-roaming, cancer-fighting nanomotor, from its introduction into the human body to the conclusion of its mission, where challenges arise at every turn.

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Nanomotors encounter a hostile immune system that actively clears away nano- and microparticles of diverse sizes and materials after surviving the protein coating and high ionic strength. According to a recent survey [14], fewer than 1% of nanoparticles used in targeted cancer therapy make it to the tumor before being cleaned out of the body, and this figure likely applies to nanomotors as well. Nanomotors must be manufactured from more biocompatible materials and in appropriate sizes and shapes to enhance their chances of survival. Fortunately, material chemists can learn a lot from the huge body of research on nanomedicine. [98-101] Furthermore, recent advancements have opened up new possibilities for nanomotors to avoid detection by the immune system, such as coating nanomotors with red blood cell membranes, platelets, [15, 11, 116], and liposomal vesicles, [17], utilizing nanomotor-microorganism hybrids [118-120], and cell-based motors, [121, 122], as well as a better understanding of how motor structure affects its performance. [115]

Despite the numerous appealing characteristics chemically powered nanomotors may provide, the various obstacles described in this section, which arise seconds after the nanomotors are injected into a human body, chemically powered nanomotors are essentially ruled out for any missions in blood streams. This is a harsh conclusion because it contradicts a large body of published research that claims otherwise.However, a deeper examination reveals that the vast majority of published investigations of chemical nanomotors for biomedical applications use nanomotors that are either in vitro or move in biological fluids in a much less directed and slower manner than they would on a laboratory glass slide. Our bold conclusion that chemical nanomotors are unsuitable for blood vessel operations could be overturned pending improvements in motor designs, but for the time being, researchers who are serious about using nanomotors in targeted cancer therapy should focus on nanomotors powered by other means, such as magnetic fields, light, or ultrasound. [125-127] Section 4 delves more into the issue of selecting the proper power source.

3.2 Homing

After overcoming the initial hurdles of surviving in a hostile in-vivo environment, nanomotors are now ready to identify their target: cancer cells in a tumor in this case.This is a similarly difficult endeavor, one that comes with a slew of difficulties. A nanomotor cruising through the bloodstream is like a sluggish boat negotiating raging rivers.

Blood vessels are the ideal "white water rafting" game for a nanomachine, with a typical flow speed on the order of cm s1 and a meandering route that may be as long as 100 000 km when expanded. So, in such a frantic maze, how can a nanomotor find and reach a tumor?

The first problem is that there isn't enough electricity. [12] A quicker nanomotor not only has a better chance of beating the blood flow and getting to where it needs to go, but it can also load more cargo and apply more force. A faster mission implies the immune system has a lower probability of removing a nanomotor. Building a powerful nanomotor is therefore one of researchers' top priorities, [128-130], but we have yet to witness a nanomotor with diameters ranging from nanometers to a few micrometers moving at a speed even close to that of blood flow. Although bubble-propelled micromotors might achieve similar speeds, they still suffer from the protein corona problem discussed above, and create bubbles that could be hazardous to humans.

Is it possible to make motors bigger and therefore more powerful? After all, scaling things up is far easier than scaling them down, but at the cost of quicker clearance from the body and ineffectiveness in reaching the intended tumor location. Much earlier research on nanomedicine suggests a nanoparticle size of 100 nm [114], but machines this small would have limited steerability [131], rendering them useless when immersed in blood streams.Poor navigation is especially problematic for nanomotors smaller than micrometers, when Brownian motion takes precedence over active propulsion. This means that, even if the nanomotor is powerful enough to counteract blood flow, it will follow entirely random trajectories, similar to a deflated balloon, and will very certainly miss its goal.

A guiding strategy becomes critical at this point, and two widely used approaches have been proposed in the literature. The first and most common technique is to include a magnetic substance in the nanomotor so that it is guided by an external magnetic field [132] for an early example). However, as the nanomotor gets smaller, the necessary magnetic field gradient grows larger, necessitating a cumbersome and dangerous magnetic setup. A second approach, known as chemo/photo-taxis, borrows from biology, in which a gradient of chemicals or light induces a swarm of bacteria or algae to move collectively. [133, 134] The commonly held belief is that, since the concentration of protons, oxygen, and other chemicals around tumors differs from that in normal blood, a nanomotor may respond to this chemical gradient and chemotaxi to its target without the need for human involvement. [135] Although this biomimetic concept is intriguing and has been proven in vitro, we are unaware of any effective in vivo demonstration. A naive counter-argument is that, assuming the gradient exists, it must be very weak in human bodies, such that a nanomotor would not be able to respond strongly enough to be successfully directed.

Finally, a nanomotor that is actively navigating through a maze of blood arteries in pursuit of its goal requires some kind of imaging technology to either check that it is on the right track or to give visual assistance to the human operator to guide the motor. Fluorescent imaging, [23], 137, 138, ultrasonic imaging, [139], 140 magnetic resonance imaging, photoacoustic computed imaging, and radionuclide imaging have all been used to view and track nanomotors in real time. [142] Because a single nanomotor is significantly smaller than the resolution of any available medical imaging technology, researchers have recently focused on imaging 1) a swarm of nanomotors, [29, 143]. 2) motors that are considerably bigger than nano- or micrometer scales, or 3) motors that use bubbles or photoacoustic agents to enhance image signals [144]. However, we should emphasize that imaging methods are rapidly improving (fueled by requests from a wide range of applications). As a result, we believe it will be beneficial for imaging of medical nanorobots, and that this issue will not stymie their clinical application.

Although real-time 3D tracking of nanomotors using medical imaging techniques is still in its early stages (with hopeful progress), researchers should seriously examine this issue before claiming the therapeutic effectiveness of their nanomotor designs. Otherwise, even if a nanomotor travels effectively in vitro and aggregates at the correct location in vivo, it might end up floating "dead" in blood flow, like its inactive cousins reported in multiple nanomedicine investigations. Seeing is believing, after all.

3.3 Execution

A nanomotor, no matter how fast, steerable, or biocompatible it is, is useless unless it accomplishes its goal. This translates to moving through a gel-like tumor microenvironment, releasing anti-cancer medicines when the timing is appropriate, accessing cancer cells when necessary, performing micro-biopsy, and other therapeutic activities in the case of targeted cancer therapy.

The vascular endothelium, which physically separates the blood stream from the tumor tissue, must first be passed by a nanomotor. This is thought to be possible because of the increased permeability and retention effect (EPR), which occurs when blood capillaries in a tumor leak. However, a new study shows that this impact is less significant than previously thought. [146] Nanomotors at the periphery of a solid tumor must penetrate deep inside it once cleared of this physical barrier, which is surmountable for nanoparticles of the proper size, so that all cancer cells, even those developing at the tumor's center, can be obliterated. Otherwise, relapse is a distinct possibility. In fact, one of the most pressing issues confronting drug-loaded nanoparticles in traditional nanomedicine is this. [105] A nanomotor with active propulsion is expected to outperform its passive counterpart if powered by a powerful engine with significant thrust.

However, an engine can not address all issues, particularly when the thick, viscoelastic, gel-like extracellular matrix found within a tumor is taken into account. [102] Experimentalists are currently considering nanomotor propulsion in viscoelastic media, [147-149], and have even coated the nanomotor surface such that it liquifies the gel or becomes super-slippery as it goes along. [28, 149] Even though there is reason to be optimistic about nanomotors with appropriate sizes, surface functions, and sufficient power, we have yet to see effective propulsion of a nanomotor in a legitimate tumor model, let alone in in vivo demonstrations.

Controlled drug release is perhaps the most explored and successful issue in the field of nanomotors for biomedicine (see the review articles mentioned in Section 2). The concept is similar to that of a passive nanoparticle in that a change in the particle's structure, morphology, chemical composition, or chemical reaction is triggered by either a change in the local environment (such as pH, temperature, and concentrations of other relevant chemicals) or an external cue (such as electromagnetic waves, light, ultrasound, or a combination of them). In this way, nanomotor development is built on the shoulders of decades of nanomedicine research.

A nanomotor can conduct additional physical activities, such as photothermal heating [150] or micro-biopsy, in addition to chemotherapy. [96, 151] When irradiated with light of appropriate wavelengths, a nanomotor coated with gold nanoparticles, for example, may heat up the surrounding tissues via surface plasmon resonance. However, this would need light to penetrate deep into the tissue in the first place, a trait reserved primarily for near-infrared light, [129, 152-154], posing a design limitation for nanorobots. A nanomotor may also rotate or spin (i.e., a "nanorotor" or a "nanodrill"), which is a unique characteristic that allows mechanical actions not possible with passive equivalents. Although preliminary experiments have demonstrated that nanomotors and the fluid flows they generate may mechanically interact with tissues and cells, we have yet to witness silver bullets fired into cancer cells or precise tissue-cutting in vivo.

Finally, many of the proposed actions are beyond the capabilities of a single nanomotor, necessitating the collaboration of a coordinated population, [56-59] a research topic that has received a lot of attention in recent years.Apart from the classic problem of controlling a large number of individually moving entities, a topic known as "swarm control" in the robotics community, [160], scientists are also interested in the complex interplay between chemical, electric, magnetic, and hydrodynamic fields within a group of nanomotors. Emergent behaviors [1601, 162] are typically the result of these many-body interactions, which are scientifically intriguing but technically challenging, and are consequently investigated for basic knowledge rather than practical applications.

Unfortunately, many studies only reveal the biomedical functions of one or a few nanomotors, implying that whatever one nanomotor is capable of, whether medication delivery or microbiopsy, will happen a billion times more or better for a group of a billion nanomotors.As P. W. Anderson brilliantly explains in his classic article "More is different," this isn't always the case. [163] In terms of statistical significance and data repeatability, this approach of reporting merely a few nanomotors is likewise not advised.

For a set of externally driven nanomotors, such as those powered by magnetic fields or ultrasound, the concept of "swarm control" may be easier to execute. [29, 164] Externally applied fields (and hence forces and torques) induce a nanomotor group to move in unison at comparable speeds and directions in these systems. This characteristic, on the other hand, is a double-edged sword since it allows for easy coordination across a huge population while missing individual control/activation and the complex interactions among nanomotors that might be critical in particular activities. Biomimetic techniques for synchronizing a group of chemically oscillating nanomotors have been developed [165], but they, too, suffer from the same problems that plague chemically driven nanomotors in vivo, and are thus unlikely to be practicable for the purposes addressed in this paper.

3.4 Completion

When a nanomotor completes its job, such as delivering medicines to cancer cells, a great journey comes to an end. These nanomotors, which are now imprisoned deep inside and dispersed across a solid tumor, must be properly removed from the human body. Perhaps the easiest approach to achieving this is to create nanomotors out of biodegradable materials that decay into harmless compounds over time. [166-168] Many publications on biodegradable drug-delivery nanoparticles, such as those composed of poly (lactic-co-glycolic acid) (PLGA) or polyethylene glycol (PEG), would lead one to believe that this is a simple task.

However, effective nanomotors are frequently constructed from a small number of components. [50] Chemically driven nanomotors, for example, are typically (but not always) composed of noble metals like gold (Au) and platinum (Pt), which accelerate the breakdown of H2O2, or chemically active metals like aluminum (Al) and magnesium (Mg), which react with water to create gas bubbles. For various reasons, oxides such as TiO2, SiO2, and MnO2 are also desirable materials for chemical nanomotors. Materials for externally powered nanorobots, on the other hand, are more diverse. The foundation material for nanomotors driven by a magnetic field can be any of a number of materials, but to enable magnetic actuation, a magnetic material, generally nickel (Ni) or iron oxide, must be coated on the particle surface or incorporated within. Early examples of ultrasonically propelled nanorobots are generally composed of metal or metal oxide with a big enough acoustic contrast factor to permit effective propulsion, and they are becoming increasingly popular [125-127]. Few of the materials listed above can breakdown spontaneously into non-toxic compounds. Recent advances in this field, such as bubble-filled polymer nanomotors [169, 170] and acoustic liquid metal nanomotors [171], are encouraging.Although functioning and totally biodegradable nanomotors are theoretically conceivable, there have only been limited actual demonstrations [166-168], and they are frequently insufficiently strong to resist blood flow.

Terminating nanorobots can also include retrieving them from human bodies and even recycling them for future usage. However, given the challenges of guiding them out of the depths of a tumor, through blood arteries, to a certain rendezvous place where a device can ultimately remove them, this becomes even more technically demanding. Alternatively, we might delegate the task of "trash removal" to the body's immune system, but this proposal may run counter to the original objective of developing nanomotors with extended retention times. In any case, we need to minimize the number of nanomotors imprisoned inside our bodies as much as possible, which necessitates better nanomotor efficacy in the same vein as focused medication release.

Finally, we should consider if we really need to get rid of these nanomotors. For example, it would be beneficial if they could remain in our bodies after completing their primary job as a surveillance/sensing/dormant surgeon. Alternatively, even if they become worthless, it may be OK to leave them where they are if the amount of hazardous materials is low: 1 billion Au nanowires commonly employed as ultrasonically driven nanomotors weigh on the order of 1 mg, according to a preliminary estimate. Nanomotors' potential toxicity, particularly in amounts relevant to their real biological use, is unknown. This topic is undoubtedly linked to the critical issue of nanomotor biocompatibility, which has been discussed elsewhere. [66]

4 Powering Nanomotors in Vivo is a significant challenge.

Throughout the aforementioned voyage of a medical nanorobot, it became obvious that there are significant gaps between the published state-of-the-art and a clinical product for targeted cancer therapy. Among the numerous scientific and engineering problems we've discussed, we believe there's one that "rules them all": determining the proper propulsion principles for a nanomotor to function in vivo. In fact, we believe that answering this issue comes before designing a nanomotor that operates in blood vessels—and, in particular, targeted cancer therapy—and determines the operation's success, regardless of how effective other elements of it appear to be.

To elaborate, active propulsion is essential for many of a nanomotor's touted benefits, but its effective application to human bodies is difficult. We note in particular that few, if any, state-of-the-art chemically powered nanorobots are suitable for operations involving blood streams and intracellular environments, regardless of whether they are made of polymers, metals, oxides, or enzymes, [172] and whether they are powered by H2O2, glucose, water, or other biocompatible/toxic chemicals. Some of these constraints are self-evident, such as the creation of bubbles in the blood and the fast production of protein corona, while others are more subtle and relate to the specifics of a propulsion system (e.g., phoresis-based mechanisms work poorly in salt solutions). [173]

Furthermore, under physiologically relevant circumstances, chemical nanomotors are generally extremely weak (speeds on the order of tens of body lengths per second or less) and difficult to regulate (in speeds, directionality, etc.). The problem of accurate control is exacerbated by shrinking them to the sizes necessary for targeted cancer therapy. Because we don't see a quick answer to any of the aforementioned difficulties, chemically powered nanomotors—regardless of whether they're powered by phoresis or bubbles—are ill-positioned as nanorobots for targeted cancer therapy, at least for the time being. They are, nevertheless, perfectly warranted in other biological applications, such as those recently proven in stomachs or intestines [16-18, 85], although these scenarios are outside the focus of this article.

So, are externally driven nanomotors, such as magnetic fields and ultrasound, the saviors? Not quite, or not quite yet. One of the primary drawbacks of these nanomotors is that they rely on external power and direction rather than fuelling themselves from the local environment, which necessitates a large and complex external setup. Most documented ultrasound-powered nanomotors, for example, need an acoustic setup that generates standing waves of MHz moving within a cavity of a particular thickness [174], which is difficult to achieve in vivo (although the very recent development of streaming-based nanomotors via traveling sound waves has largely mitigated this issue [169, 170, 175]). Magnetic nanomotors have the same difficulties as other complicated equipment. Furthermore, the nature of external actuation usually results in a swarm of nanorobots moving in unison (picture a marching band), rather than moving individually. When nanomotors need to navigate and operate in restricted areas, such as the tumor microenvironment, this might become a major problem.

Alternatively, using the asymmetric heating of a specifically coated colloidal particle under light, the photothermal effect has recently emerged as a promising approach for powering nanomotors in vivo. Self-thermophoresis [176], or demixing a binary liquid, was used in early research in the physics community to show the autonomous propulsion of gold-coated microspheres under laser irradiation. [177] Self-thermophoresis, in which a colloidal particle moves along its own temperature gradient, has recently been used to power polymer microtubes, carbon nanoparticles, and silica nanoparticles in vitro [129, 152, 178], as well as silica nanoparticles in vivo [154], all using near infrared light with a high penetration depth and good biocompatibility. The key to this sort of nanomotor's success, however, may be finding a careful balance between a high enough power density to operate a nanomotor at a respectable speed while being biocompatible. Furthermore, the problem of directing these nanomotors in a complicated environment while using near-infrared light is still being worked out.

Externally driven nanomotors, on the other hand, have the benefit of being able to be coated with biocompatible materials such as polymers or even red blood cell membranes due to the lack of surface chemical interactions. [87] As a result, they are less vulnerable to immune system assaults and are less affected by the protein corona effect.

Externally powered nanorobots, when combined with their high speeds, offer more potential for the function of nanomotors, awaiting more research and development. Biohybrid nanomotors, which were recently introduced, offer an intriguing alternative to non-biocompatible power sources. [118-120, 179] A biohybrid nanomotor, as the name implies, combines a synthetic, functional component with live microorganisms such as bacteria, algae, macrophages, and spermatozoa that move independently in aqueous solutions without the need for human involvement. The utilization of natural creatures, particularly those that are compatible with human bodies, substantially simplifies the process of powering a nanomotor while also providing unique benefits inherent to live organisms, such as sensing, chemotaxis, and swarm management. However, concerns like safety, immunological responses, and mass production must all be addressed. [119] In a similar way as when cyborgs stop being humans, the concept of biohybrid nanomotors contradicts the concept of "synthetic microswimmers," which is widely believed to be the essential attribute of nanomotors in the current context.

5 Final Thoughts

Cancer-fighting, blood-roaming Nanorobots, like many other emerging technologies, have the potential to transform our lives, but they have yet to demonstrate their use in real-world settings. We've described the requirements for a nanomotor to survive the in vivo environment, locate its targets, operate as needed, and terminate when the mission is complete, using targeted cancer therapy as an example and focusing on synthetic microswimmers in the nanometer and micrometer regime (i.e., "nanomotors"). We highlighted important basic and technological problems, introduced state-of-the-art development in different aspects, and remarked on the possibility of these advancements in overcoming the urgent concerns by following the footprints of a nanomotor in this SLOT mission. We find that nanomotors driven by chemical gradients (i.e., phoresis-based) are salt-sensitive and slow, whereas microjets generate gas bubbles that are incompatible with blood streams (especially when a large number of motors are involved).Despite our optimism about advances in nanotechnology and material chemistry, these issues appear to be firmly woven into the propelling mechanism of chemical nanomotors. As a result, until a breakthrough occurs that ushers in an entirely different mechanism, chemically driven nanomotors are not suited for targeted cancer therapy, no matter how dismal they may appear.

Is there such a thing as a perfect nanomotor (at least for cancer treatment), and if so, what would it look like? This is arguably the first and most important topic we should consider, and we should consider it carefully. This article has already identified a number of essential qualities that are necessary for achieving this aim, as well as designs that lack them. As a basic design concept, we anticipate a nanorobot that is the appropriate size, made of biocompatible or biodegradable materials, and capable of rapid, autonomous propulsion through a maze-like network of blood arteries at a flow rate of about cm s 1.

This nanomotor must also locate the tumor, navigate inside its depths, and release therapeutic chemicals when the moment is appropriate, all while inflicting the least amount of damage feasible. Finally, it must detach itself from human bodies after the task is completed. These qualities, as appealing as they are, set a very high bar for nanorobot development, one that may be too high to attain in the near future.

However, in the spirit of constructive criticism, we propose the following hypothetical, idealized nanomotor design that follows the above blueprint and is inspired by the good and bad aspects of state-of-the-art nanomotors. To begin, we envisage a nanomotor that is either a microcapsule with a trapped gas bubble that is powered by MHz frequency traveling sound waves or a magnetic microparticle that travels in a rotating magnetic field. Two examples of the latter design are a helical nanowire that swims by rotating its body [24], 180], and a microsphere that rolls on the surface of blood arteries.[30] Both of these power sources, ultrasonic and magnetic fields, are essentially biocompatible and avoid many of the complications we've discussed so far. This nanomotor is 100–1000 nm in size, tiny enough to move in a complicated tumor microenvironment and across endothelial junctions, yet large enough to be controlled and observed using next-generation imaging methods (we take a leap of faith here and trust that the recent fast development of imaging techniques will continue). The nanomotor is constructed of biocompatible polymer (e.g., PLGA or PEG) with an optional iron oxide coating to enable magnetic propulsion/steering, and it is further covered on the exterior with blood cell membranes or platelets to reduce immunological reactions. Therapeutic substances, such as anti-cancer medicines or genetic elements, are embedded inside all of these levels. To release them, a mechanism must be in place to remove (or generate pores in) the cell-mimicking coating on demand, which may be accomplished by localized heating or, better yet, the photothermal action of gold nanoparticles encapsulated in the nanomotor body. It is deemed safe to keep these nanomotors within human bodies after they have completed their tasks because they are biodegradable polymers and mainly bio-inert materials.

Granted, this concept necessitates a lot of human interaction in terms of navigating and activating nanomotors, and it comes with a lot of engineering hurdles, but it's a scientifically sound solution to the SLOT problem. Other options exist, such as hybrid nanomotors that combine chemotaxis with biological propulsion, but it's unclear if this (or other) design is better or worse than the one we presented. In the future, despite the critical review we gave above, we believe that the goal of a nanomotor is achievable if we can launch a mini-Apollo mission in which, instead of sending humans to the moon, we want to send a surgeon into the bloodstream. Both are large-scale, complicated undertakings with far-reaching implications that will need the dedication, tenacity, and inventiveness of generations of scientists and engineers. We are confident that a significant transformation of the existing system is now required, because progress reported across multiple laboratories and in different areas of a SLOT mission is sometimes not only contradictory, but also poorly translatable for clinical applications.Instead, having a shared objective and working toward it will benefit the entire community, and this essay is perhaps one start in that direction.

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